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AACR 2016

T cells are immunotherapy stars, but in an ensemble performance

By Anette Breindl, Senior Science Editor

NEW ORLEANS – The annual meeting of the American Association for Cancer Research (AACR) was filled with news of the latest immune oncology progress, as cancer meetings, these days, are wont to be. But in a sign that immunotherapy is on its way to becoming an established branch of cancer treatment, those reports have become both broader and more incremental as the field has matured into one that has many facets.

Notably, immunotherapy approaches are now being explored in cell types beyond the killer T cells that are the target of Yervoy (ipilimumab, Bristol-Myers Squibb Co.), Keytruda (pembrolizumab, Merck & Co. Inc.) and Opdivo (nivolumab, Bristol Myers Squibb Co.).

Even the already approved agents likely owe some of their success to their effects on other cell types besides T cells.

THE MACROPHAGE EXPRESS

Macrophages, for example, "start to express copious amounts of [checkpoint signal] PD-L1 – as much or more as the tumor cells themselves," Daniel Flynn told *BioWorld Insight.*

Flynn is the founder and chief scientific officer of Deciphera Pharmaceuticals LLC, which has two macrophage-targeting programs.

Macrophages are innate immune cells, and like other immune system cells, including T cells themselves, can be either stimulatory or inhibitory. Deciphera CEO Michael Taylor told *BioWorld Insight* that tumors can convert macrophages from an antitumor to a pro-tumor state. "The tumor can really craft its microenvironment," he said.

The goal of therapeutic intervention is to turn the macrophages back to an antitumoral state. The company is in phase I trials with rebastinib, a Tie2 and VEGFR kinase inhibitor that is directed at Tie-2-expressing macrophages, which promote angiogenesis and metastasis.

At the AACR meeting, Deciphera presented data on its preclinical program with DCC-3014, an inhibitor of colony-stimulating factor 1 receptor (CSF1R), also known as FMS kinase, showing that the drug – which, unlike other CSF1R-targeting agents, is highly specific and does not act on even closely related kinases – turned both macrophages and adaptive immune cells to an antitumoral state, and had additive effects with PD-1 blockade in vivo. The company intends to enter the clinic with DCC-3014 in the second half of 2016.

Scientists from the National Cancer Institute also presented preclinical data showing that adjuvant therapy with Plexxikon Inc.'s CSF1R-targeting PLX3397 reduced metastatic spread in a model of rhabdomyosarcoma.

Two CSF1R-targeting antibodies are in clinical trials. Five Prime Therapeutics Inc. has a potentially billion-dollar-plus deal with Bristol-Myers Squibb Co. for its CSF1R antibody FPA008. That compound is being tested in combination with Opdivo in patients with advanced cancers. (See *BioWorld Today*, Oct. 16, 2015.)

Another CSF1R antibody, Amgen Inc.'s AMG 820, is in a phase I/II trial in combination with Keytruda in patients with advanced solid tumors.

Targeting CSF1R converts macrophages from an inhibitory pro-tumor to an inflammatory antitumor state. Jounce Therapeutics Inc., co-founded by Yervoy developer James Allison, presented data at AACR showing they were able to achieve the same inhibitory to stimulatory conversion with an antibody against the receptor TIM3. TIM3 is also expressed on T cells, but Jounce's antibody is specific to the form that is found on macrophages.

DENDRITIC CELLS

T cells get their antigens presented to them by dendritic cells, and the first successful cancer immunotherapy, Dendreon's Provenge (Sipuleucel-T), was a dendritic cell vaccine. So it is not surprising that dendritic cells, too, are direct targets of attempts to strengthen the antitumor immune response by several companies.

Dendritic cells (as well as tumor cells themselves) produce the enzyme indoleamine 2,3-dioxygenase (IDO), which metabolizes tryptophan to kynurenine. Kynurenine has a net inhibitory effect on killer T cells, and there are multiple IDO inhibitors in clinical trials.

At the conference, Newlink Genetics Inc. provided an update on a phase II trial of its IDO inhibitor, indoximod, which is being tested in combination with Yervoy, Keytruda or Opdivo in advanced-stage melanoma. Indoximod is also in phase II trials for multiple other solid tumors, including breast, prostate and pancreatic tumors.

Pfizer Inc. and Belgian biopharma firm Iteos Therapeutics Inc. presented preclinical data showing their IDO inhibitor, PF-06840003, reduced kynurenine levels by up to 80 percent in mouse models, and synergized with checkpoint inhibitors. Idera Pharmaceuticals Inc. also presented data showing synergy of IDO inhibition, in that case with TLR-9 agonist IMO-2125.

Aduro Biotech Inc. reported data on using cyclic dinucleotides (CDNs) to stimulate the STING (stimulator of interferon genes) pathway in dendritic cells, with the ultimate goal of stimulating killer a T-cell response.

The team found that its CDN ADU-S100 was effective at both inducing tumor regression and protecting against recurrence in animal models, though doses that were either too low or too high were ineffective against regression and recurrence, respectively. Aduro CEO Thomas Dubensky told *BioWorld Insight* that STING "is a central node of innate immunity that results in developing an adaptive immune response."

Dendritic cells may also be behind the immuno-oncology effects of cells that are not immune cells, or human cells, at all – the bacteria of the gut microbiome.

The interplay between commensal microbes and cancer is becoming "quite impactful," University of Chicago professor of pathology and medicine and Jounce co-founder Thomas Gajewski told the audience at a session on "Microbiome and Cancer Immunotherapy."

At the session, Leticia Corales, who is now a research scientist at Aduro, described experiments she and her colleagues did in Gajewski's laboratory to probe differences in the antitumor immune response that can be mounted by different mouse strains.

The team investigated the effects of the gut microbiome on the antitumor immune response of mice from the Jackson laboratories, which have a robust antitumor immune response, to those from another company, Taconic Biosciences Inc., which have a weaker response.

In fecal transplant experiments, fecal matter from Jackson labs mice had a dominant effect and could improve antitumor immune response in Taconic mice.

Corales said that in the experiments, bifidobacterium showed the highest correlation with strong T-cell responses. Signals upstream of T-cell activation enhanced T-cell effector function, which points to an effect of host dendritic cells, though the pathway from bifidobacterium to more active dendritic cells is still unclear.

Laurence Zitvogel, research director of tumor immunology and immunotherapy at the French Institut Gustave Roussy, described research by her group showing that microbiome composition affected the response to checkpoint inhibitor Yervoy.

"We bear in our guts some immunogenic commensals that are mediating immunosurveillance and enhancing the response to therapy," she told the audience – a concept she termed oncobiotics.